*Epileptic Disord 2006; 8 (Suppl. 2): S67-76*

# Towards a definition of the "practical" epileptogenic zone: a case of epilepsy with dual pathology

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**ABSTRACT –** Presurgical evaluation for patients with drug-resistant epilepsy requires the definition of various zones that have a variable spatial relationship with the epileptogenic zone. All the available mehods to directly measure the actual seizure-onset zone and to define "the minimum amount of cortical tissue that must be resected to produce seizure-freedom" have significant limitations. We report on the case of a patient with dual pathology (hippocampal sclerosis and a post-traumatic scar) and discuss the contribution of the various presurgical investigations that led to surgery and seizure-freedom.

**Keywords:** epileptogenic zone, epilepsy-surgery, stereo-electroencephalography, depth recordings, dual pathology

In order to define the **"practical actual" epileptogenic zone** at each step of the pre-surgical evaluation (Lüders *et al.* 2006), a hypothesis has to be made based upon the anamnestic ictal phenomenology, clinical ictal phenomenology, scalp interictal and ictal video-EEG recordings, anatomical and functional brain neuroimaging findings. The hypothesis raised at each step may have to be modified on the basis of information provided by the next step of the investigation. Thus, the clinical-electroencephalographic-anatomical-functional correlations lead the clinician to construct a hypothesis based upon the "theoretical" and "practical" epileptogenic zone. In some cases, such a hypothesis needs to be confirmed by depth recordings; the stereo-EEG method is based on the tailored implantation of depth electrodes (see Kahane *et al.* 2006). During the pre-surgical evaluation, the following five areas (Carreño and Lüders 2001) are measured using different diagnostic techniques: the **irritative zone** ("area of cortex which generates interictal activities"); the **seizure-onset zone** ("area of cortex that initiates clinical seizures"); the **symptomatogenic zone** ("area of cortex which,

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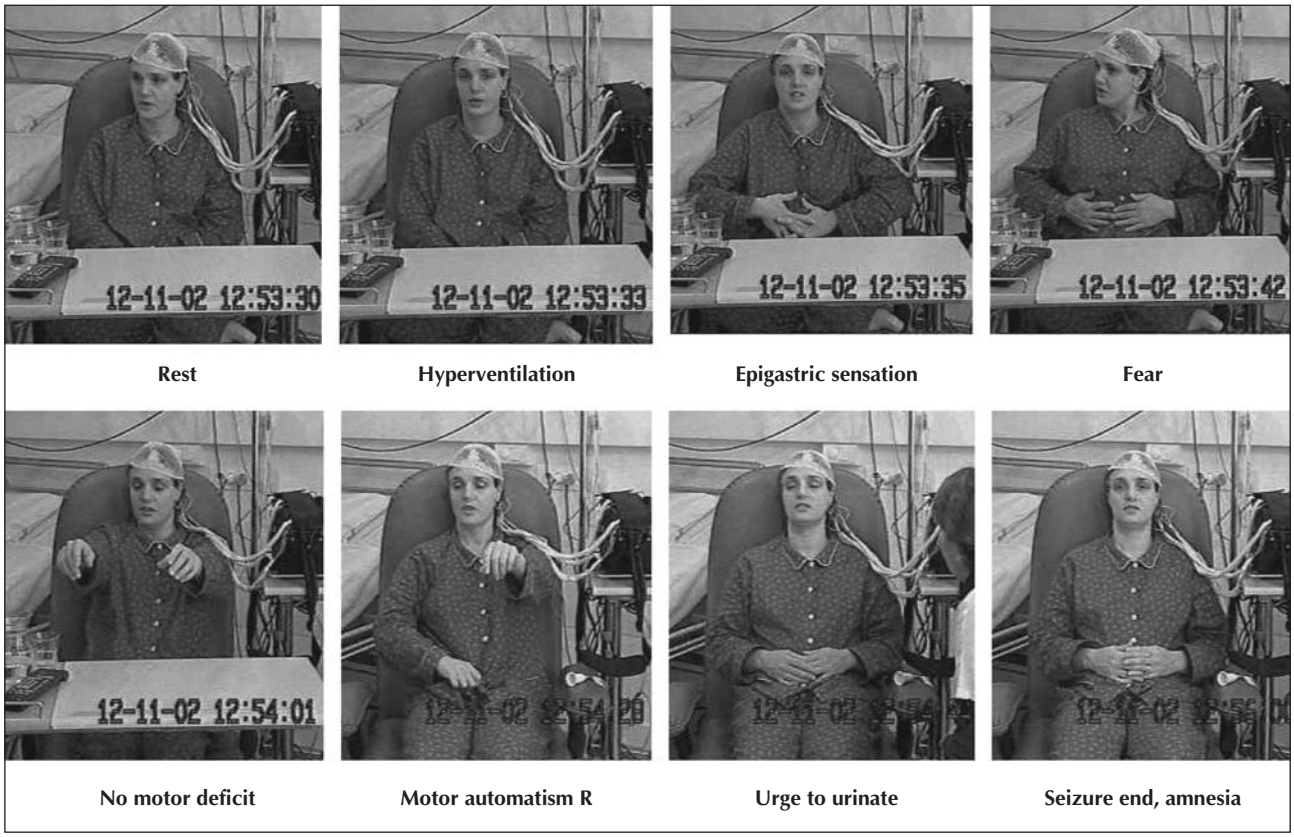



**Figure 1.** Seizure semiology.

when activated, produces the initial ictal symptoms or signs"); the **epileptogenic lesion** ("macroscopic lesion which is causes the epileptic seizures by secondary hyperexcitability of adjacent cortex"); the **functional deficit zone** ("dysfunctional area of cortex during the interictal period, producing neuropsychological deficits"). The team in charge of the pre-surgical evaluation uses this information to suggest the location and extent of the practical, epileptogenic zone. We report on a case with dual pathology, illustrating this step-by-step procedure of the pre-surgical evaluation.

## Anamnesis and seizure phenomenology

*Marceline* is a 34-year-old, right-handed, female patient. There is no family history of epilepsy, or any personal history of febrile seizures. At the age of three years, she presented an acute, symptomatic seizure after a severe head trauma. She then remained seizure-free for more than 20 years. At 27 years of age, she started experiencing episodes described as an epigastric aura, a sensation of fear, polypnea, right-hand automatisms, verbal automatisms, urge to urinate, without loss of contact. There was no post-ictal aphasia, no prolonged confusion, but amnesia of the seizure event was frequent. Despite several antiepileptic drug trials (carbamazepine, oxcarbazepine, levetiracetam, topiramate, lamotrigine), on monotherapy or in combination, the frequency of the seizures varied from four to 10 per month.

*What can we learn at this stage from the analysis of the symptomatogenic zone?*

*Can we formulate an hypothesis on the "practical" epileptogenic zone?*

### Symptomatogenic zone: initial onset and propagation signs

*Epigastric aura and fear*, although rarely reported in extra-temporal epilepsy, they are frequently associated with a symptomatogenic zone in the hippocampo-amygdalo-insular network (Fried *et al.* 1995, Kotagal *et al.* 1995, Maillard *et al.* 2004).

*Polypnea* can also be related to the hippocampo-amygdalo-insular network, particularly the insular cortex (Isnard *et al.* 2000, 2004; Ostrowsky 2000).

*Right-hand automatisms* suggest a symptomatogenic zone in the left hemisphere and can be related to an ictal imbalance between temporal and frontal lobe (Maillard *et al.* 2004).

*Urge to urinate* suggests a symptomatogenic zone in the non-dominant hemisphere, with an involvement of temporal or fronto-temporal regions (Baumgartner *et al.* 2000, Loddenkemper *et al.* 2003).

*Absence of loss of contact with verbal automatisms* is not specific to any lobe, but it probably suggests the absence of extended propagation towards other cortical or sub-cortical structures. (Gloor 1986, Lux *et al.* 2002, Blumenfeld and Taylor, 2003, Maillard *et al.* 2004).

*Absence of post-ictal aphasia.* Early post-ictal neuropsychological examination and modalities of recovery can provide valuable information regarding the eventual functional deficit related to the seizure onset zone and propagation. Post-ictal aphasia is usually observed following focal seizures primarily or secondarily involving the dominant hemisphere. The absence of post-ictal aphasia, although not specific, might point to an epileptogenic zone in the non-dominant hemisphere (Saint-Hilaire and Lee 2000, Maillard *et al.* 2004).

*Absence of prolonged confusion and amnesia of seizure events.* Temporal lobe seizures frequently spread to the contra-lateral hemisphere and are usually associated either with post-ictal, prolonged confusion or transient specific amnesia or isolated amnesia of part or all the seizure, even in the absence of loss of contact or consciousness during the event. It can be explained by a bilateral activation or inhibition of the Papez circuit (Gloor, 1986, Lux *et al.* 2002, Blumenfeld and Taylor, 2003).

### Hypothesis on the "practical" epiletogenic zone

On the basis of all the above arguments, the actual seizure-onset zone could be the right temporo-mesial region, with a spread to the ipsilateral insula and temporal neocortex, and to the contra-lateral hemisphere.

## Video ictal phenomenology

Four informative seizures were recorded, which were very similar to those previously described by the patient and her family *(figure 1)*. The additional observation made during review of videos was that the hand automatisms were bilateral, and in some seizures oral automatisms were present. No focal tonic or dystonic movement was observed. There was neither post-ictal confusion nor aphasia, but we were able to confirm a partial amnesia of the episode.

**Our initial hypothesis on the "practical" epiletogenic zone** is not modified following video-EEG recording of ictal phenomenology.

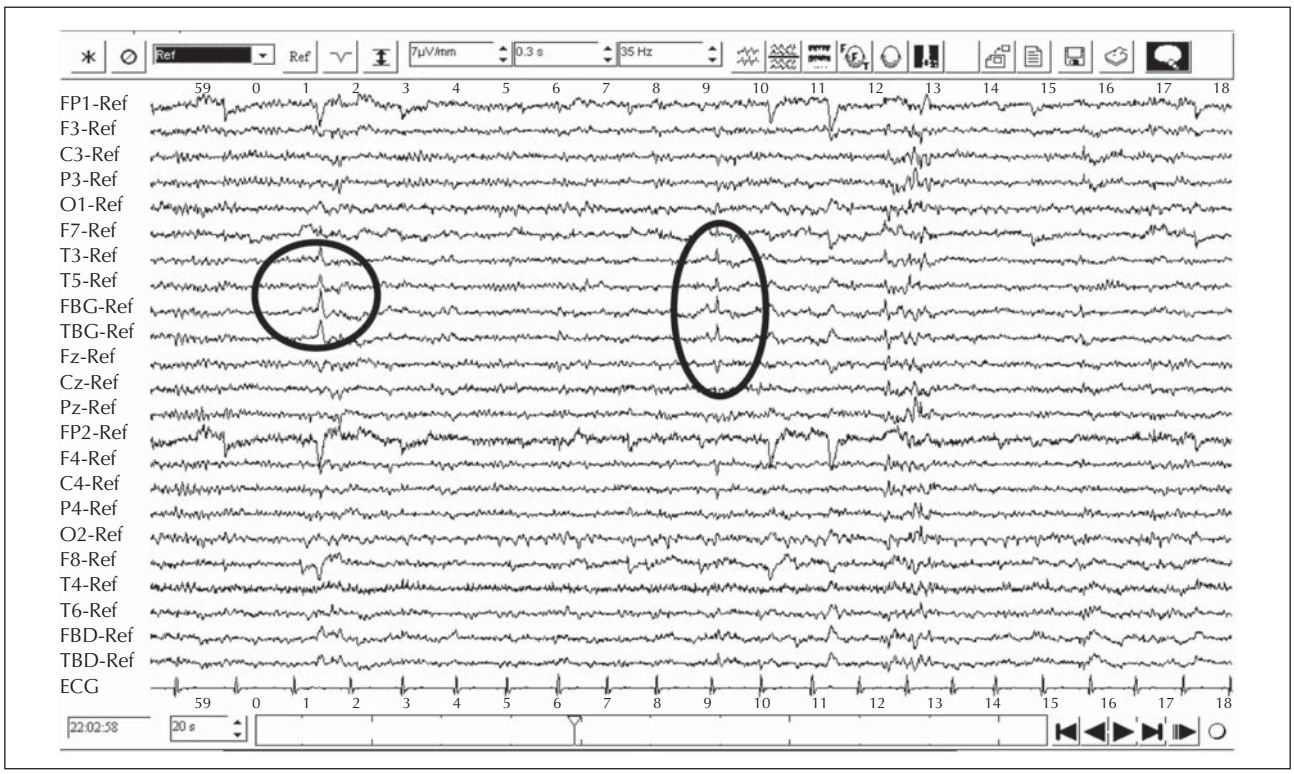



**Figure 2.** Interictal scalp EEG: left temporal spikes (circled), FBG (left frontobasal electrode), FBD (right frontobasal electrode), TBG (left temporobasal electrode), TBD (right temporobasal electrode).

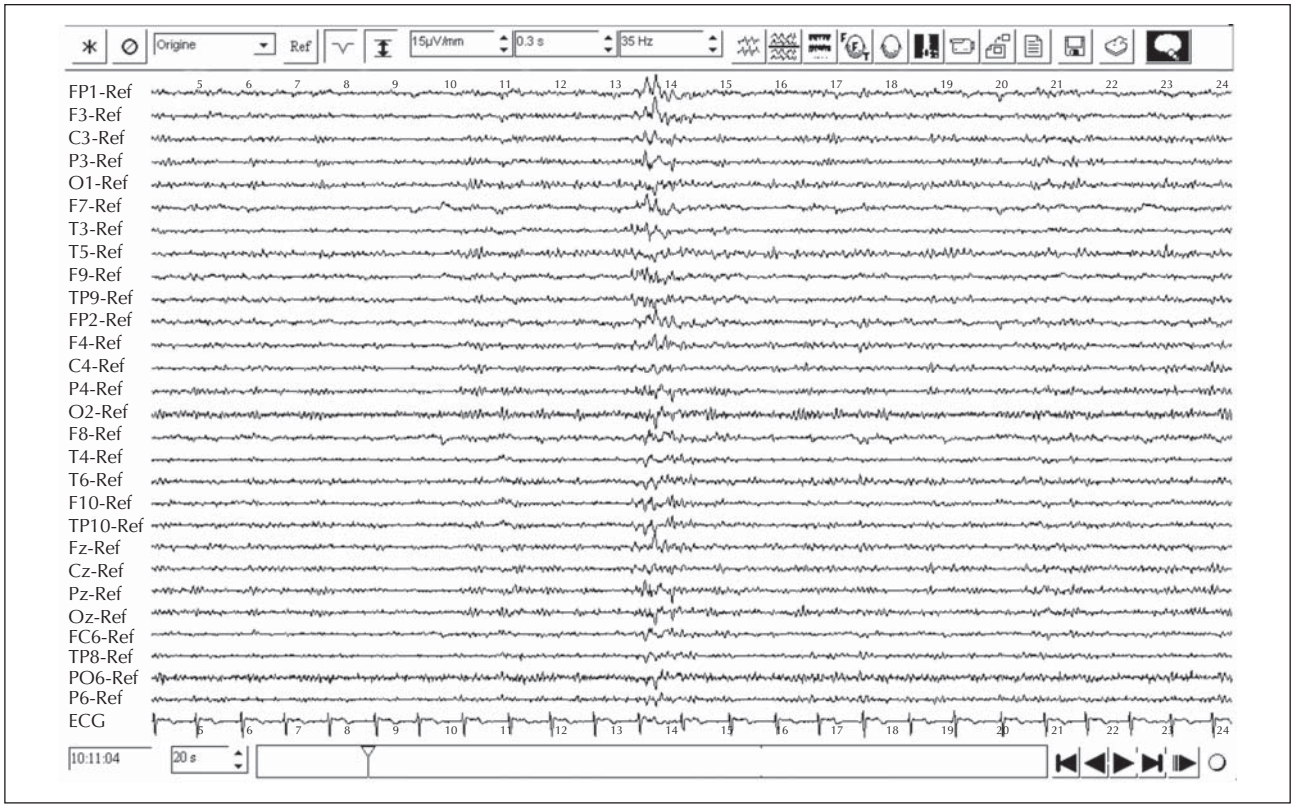



**Figure 3.** Interictal scalp EEG: bilateral sharp waves.

## Inter ictal EEG

Inter-ictal EEG (*figures 2 and 3*) showed left temporal spikes during awakening and sleep, and bilateral sharp waves.

*What additional information do we have following analysis of the irritative zone?*

*Do we have to modify our initial hypothesis on the "practical" epiletogenic zone?*

The **irritative zone** clearly involved the left temporal lobe with left temporal spikes. This was not in total contradiction with our initial hypothesis (right temporal lobe seizure spreading to the left). However, it was surprising not to find only sharp waves in the right temporal region, which was presumed to be the seizure-onset zone.

## Ictal EEG

See *figure 4*.

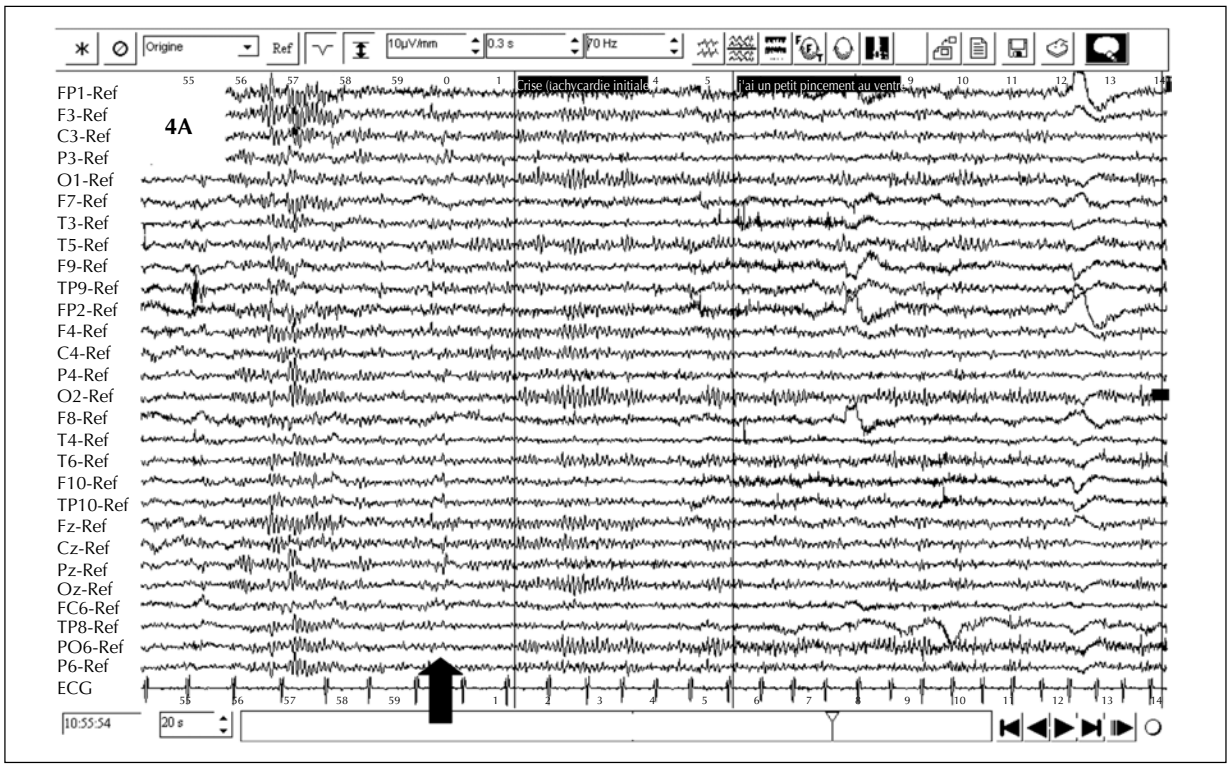
*What additional data did we obtain from the analysis of ictal EEG ?*

Although not definitive, initial depression of the EEG activity over the right temporal lobe (TP8, T4) with concomitant tachycardia was compatible with the hypothesis of a seizure-onset zone in the temporo-mesial structures. Bilateral theta activity predominating on the right hemisphere was also in accordance with the hypothesis of a right neocortical propagation followed by propagation to the left hemisphere. Consequently, at this step, our hypothesis on the "practical" epileptogenic zone is still valid.

## Structural neuroimaging MRI (epileptogenic lesion)

There was a clear, dual pathology with right hippocampal sclerosis and a right posterior, possibly post-traumatic, scar. These new elements make it difficult to known if the right posterior, post-traumatic scar could participate in the actual seizure-onset zone or in the potential seizure-onset zone *(figure 5)*.

**Figure 4.** Ictal scalp EEG: **A**) Seizure-onset, tachycardia, depression of EEG activity as regards TP8, T4. **B**) Bilateral depression of EEG activity, rhythmic theta activity on the right hemisphere. **C**) Bilateral rhythmic theta activity predominating over the right hemisphere and the temporal regions. **D**) Seizure ending on the right hemisphere. **E**) Seizure ending on the left hemisphere.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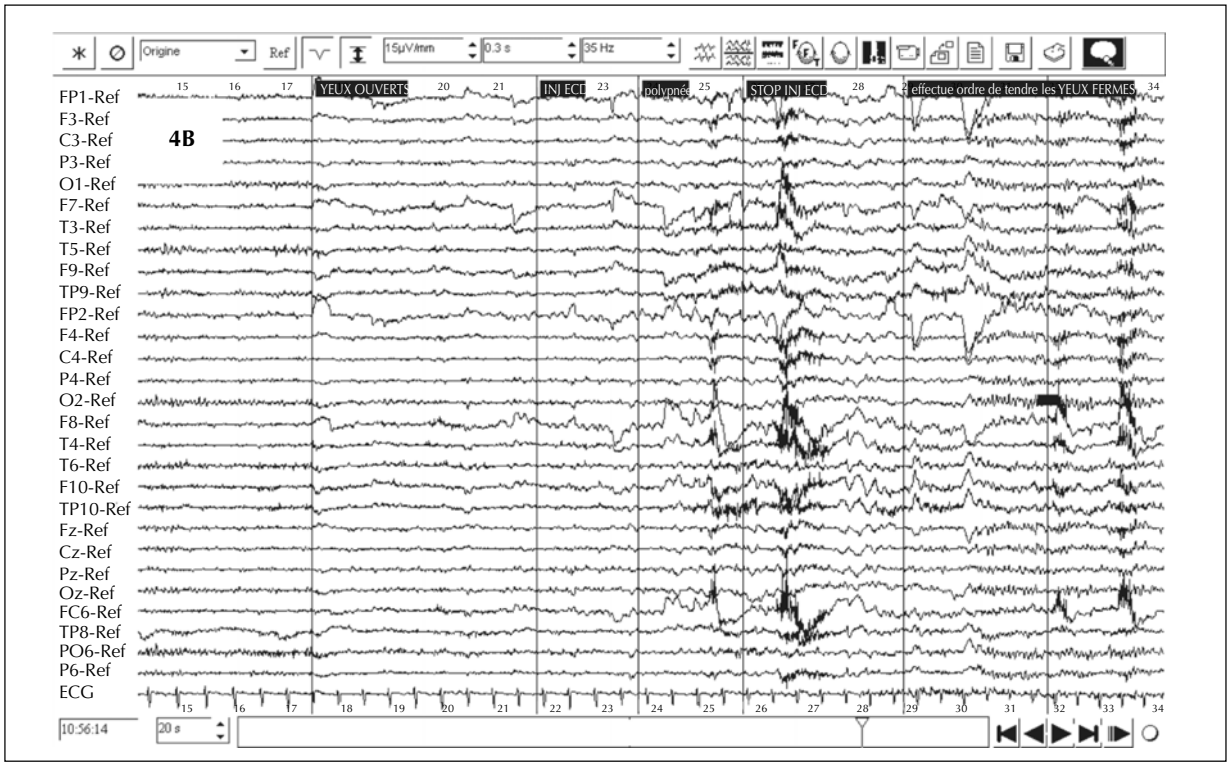
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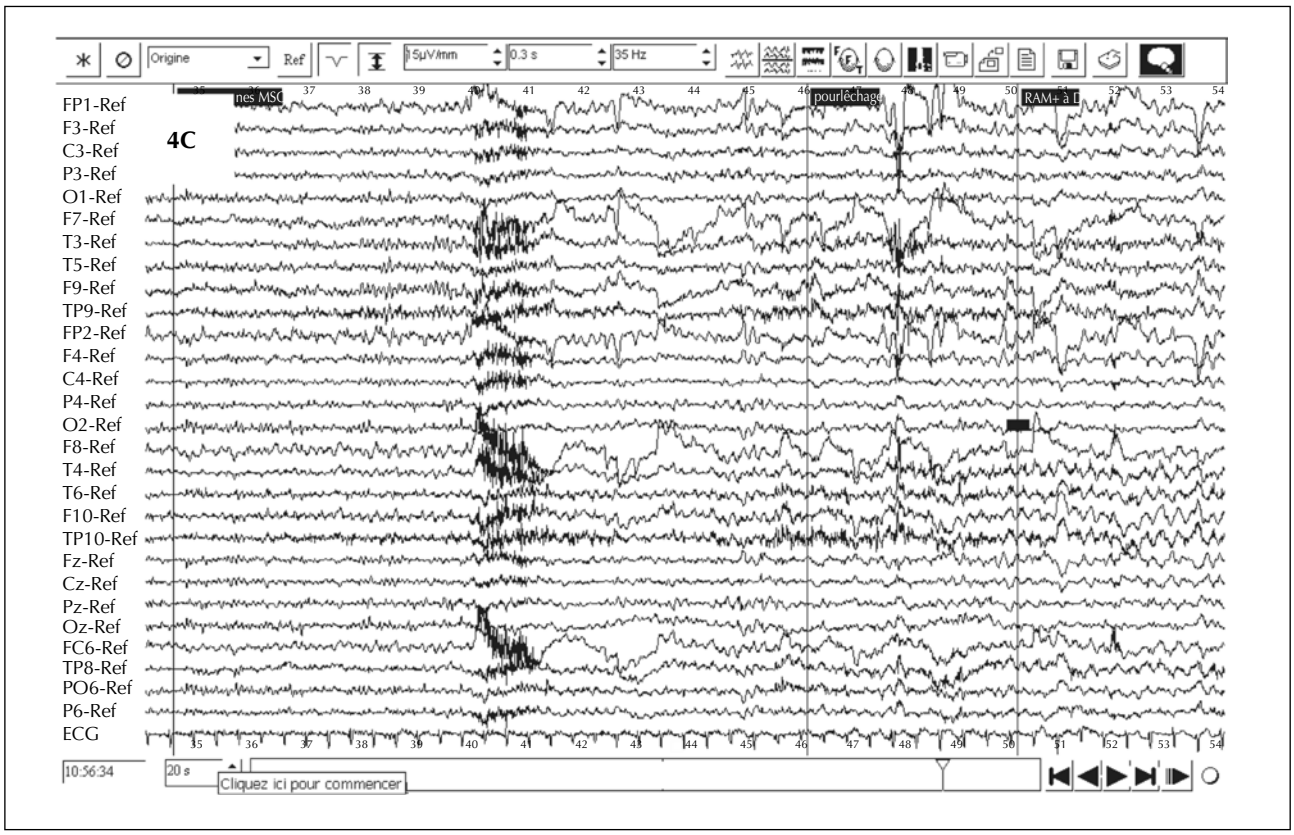
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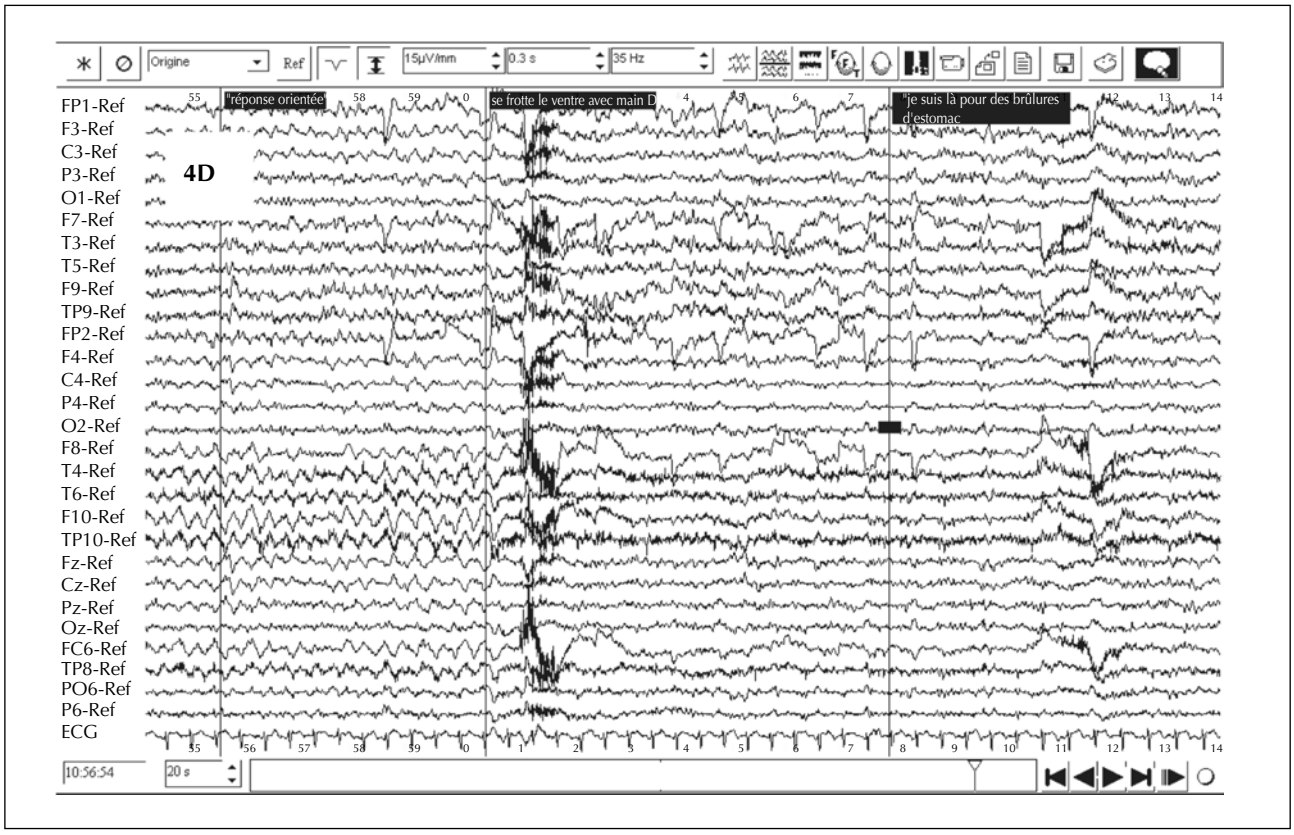
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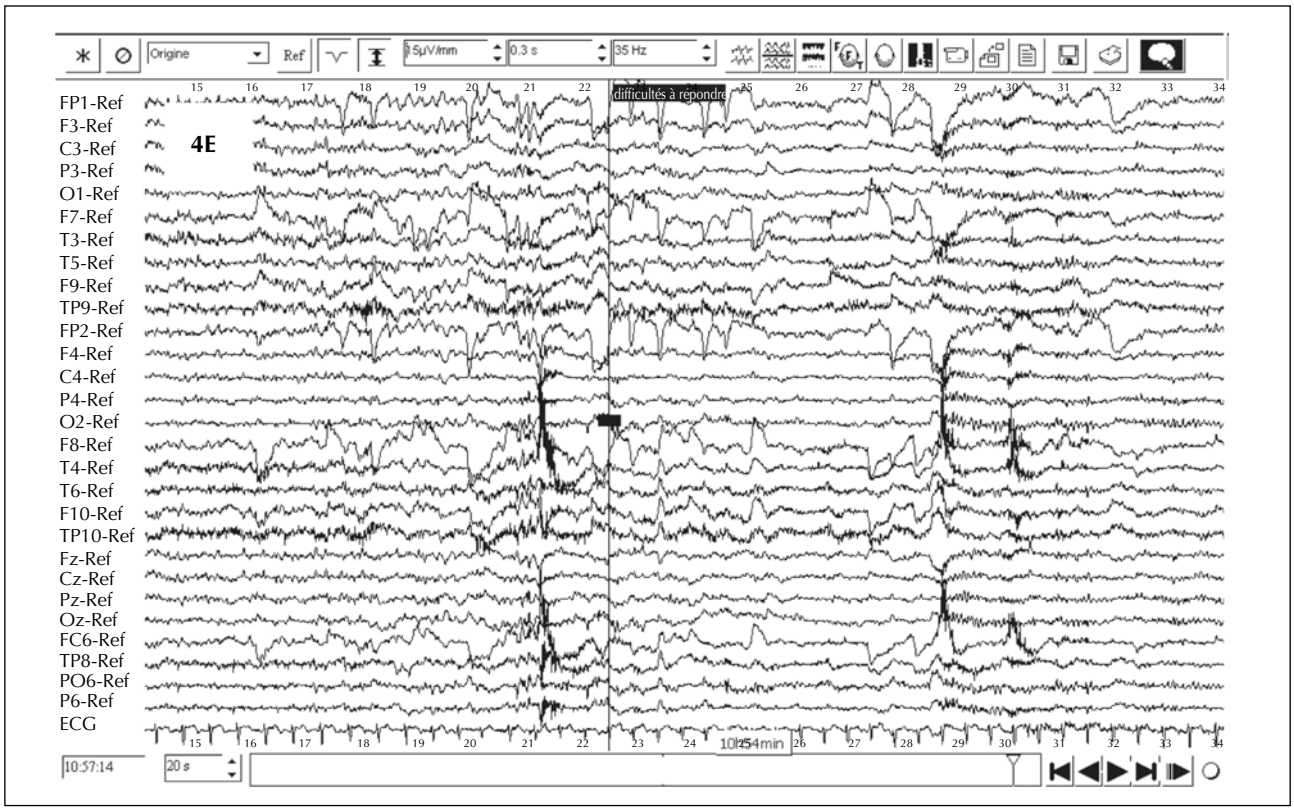


## Inter ictal and ictal SPECT
*(Functional deficit zone and actual seizure-onset zone)*

Analysis of the interictal SPECT showed hypoperfusion predominantly in the right temporo-polar and temporo-mesial regions with less striking findings in the posterior temporal neocortical region *(figure 6)*.
Ictal SPECT showed a normalization of the previously hypoperfused regions. These data are in accordance with our previous hypothesis on the prominent role of the right temporal lobe

## FDG and flumazenil PET
*(Functional deficit zone)*

The FDG PET showed a right temporo-mesial hypometabolism involving the temporal pole, amygdala and right hippocampus. Flumazenil PET shows a more limited diminution of Flumazenil fixation to the right hippocampus. These data, showing a functional deficit zone limited to right temporo-mesial structures, suggest that the actual seizure onset could be limited to right mesio-temporal structures but the potential epileptogenic zone could be larger *(figure 7)*.

## Neuropsychological evaluation and MRI spectroscopy of the temporal posterior lesion *(functional deficit zone)*

Right-handed patient; verbal IQ 80; visual IQ 96; global IQ 85; Weschler: verbal memory 91; visual memory 102. MRI spectroscopy failed to demonstrate a specific abnormality in the region of the right posterior lesion.
There was a difference between this right-handed patient verbal IQ and visual IQ. However, the Weschler test showed no major memory deficit. Consequently, we could exclude that the discrepancy between her verbal and visual IQ was related to a functional deficit of the left temporal lobe.

## Conclusions of the non-invasive phase

**Hypothesis on the "practical" epiletogenic zone:** from all the above arguments, the actual seizure onset could be the right temporo-mesial region, with a spread to the insula, temporal neocortex and the contra-lateral temporal lobe. Two possibilities were discussed:
– A right temporal lobectomy or hippocampo-amygdalectomy without further investigations;
– An invasive stereo-EEG recording in order to distinguish or differentiate the actual practical epileptogenic zone

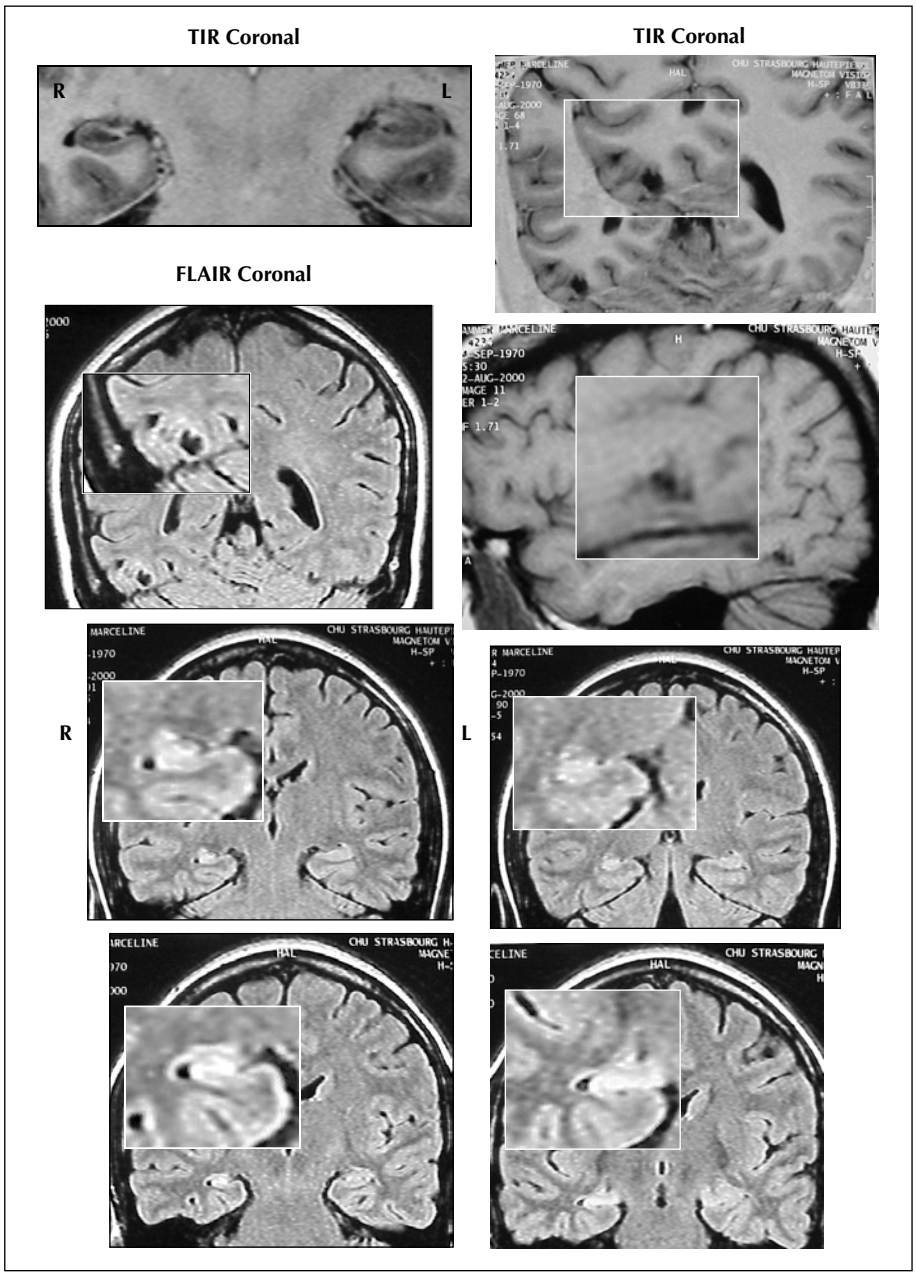


**Figure 5.** Structural neuroimaging MRI: Right hippocampal sclerosis and a right posterior post-traumatic scar.

from the potential epileptogenic zone that might also involve: the right insula, right fronto-orbital region, right posterior temporal lesion, or even the left temporal lobe. Because of the discrepancies already discussed, it was decided to perform stereo-EEG monitoring, with a tailored implantation of depth electrodes. The aim of the stereo-EEG recording was to better define the localization of the interictal EEG abnormalities, the seizure-onset zone and the early propagation zone *(figure 8)*.

## Interictal stereo-EEG data *(irritative zone)*

Interictal EEG abnormalities, spikes, poly-spikes were recorded in the right temporal pole, amygdala, anterior and posterior part of the hippocampus and para-hippocampal gyrus. Rare spikes were recorded over the left hippocampus. No SEEG abnormalities were recorded over the insula, occipto-temporal junction, fronto-orbital region.

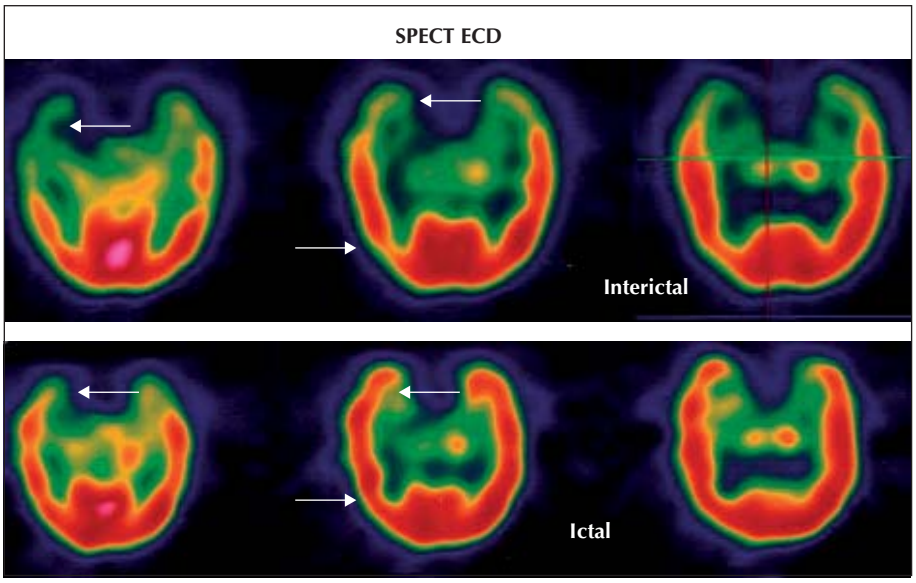


**Figure 6.** Interictal and ictal SPECT.

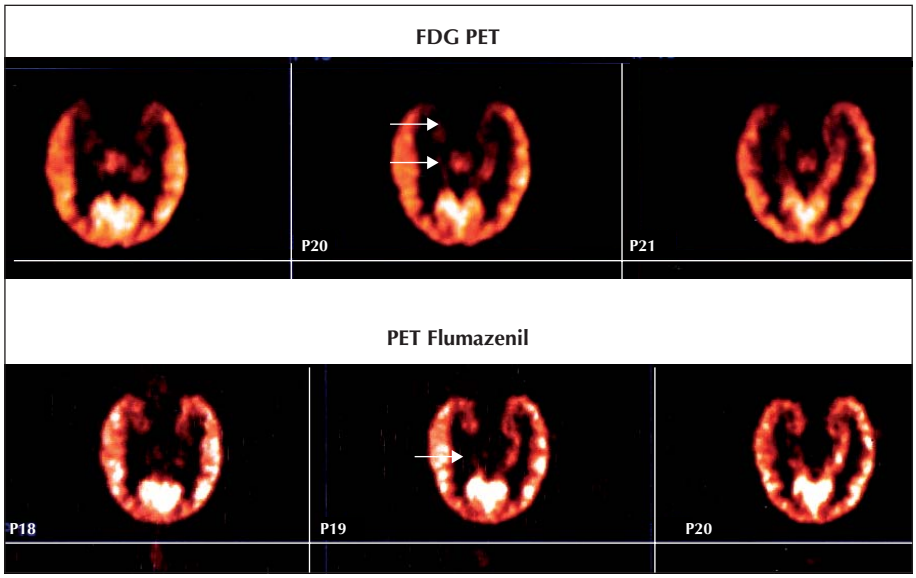


**Figure 7.** FDG and flumazenil PET.

## Ictal EEG data *(actual seizure-onset zone and early propagation zone)*

The seizure-onset zone involved, the amygdala, anterior hippocampus, right temporal pole and the anterior part of the temporal neocortex. Within 30-40 seconds, there was propagation to the fronto-orbital region and left hippocampus. Fast activity of low voltage, being probably indicative of the "actual" seizure-onset, was only seen in the amygdala-hippocampus-temporal pole complex, while the insula and the lesion (the occipito-temporal junction) were secondarily involved (60 seconds later), mostly on a slow mode of discharge.

## Conclusion

Stereo-EEG recordings allowed to further investigate the "potential epileptogenic zone" during pre-surgical evaluation (Carreño and Lüders 2001). The "actual epileptogenic zone" was considered to be limited to the right anterior

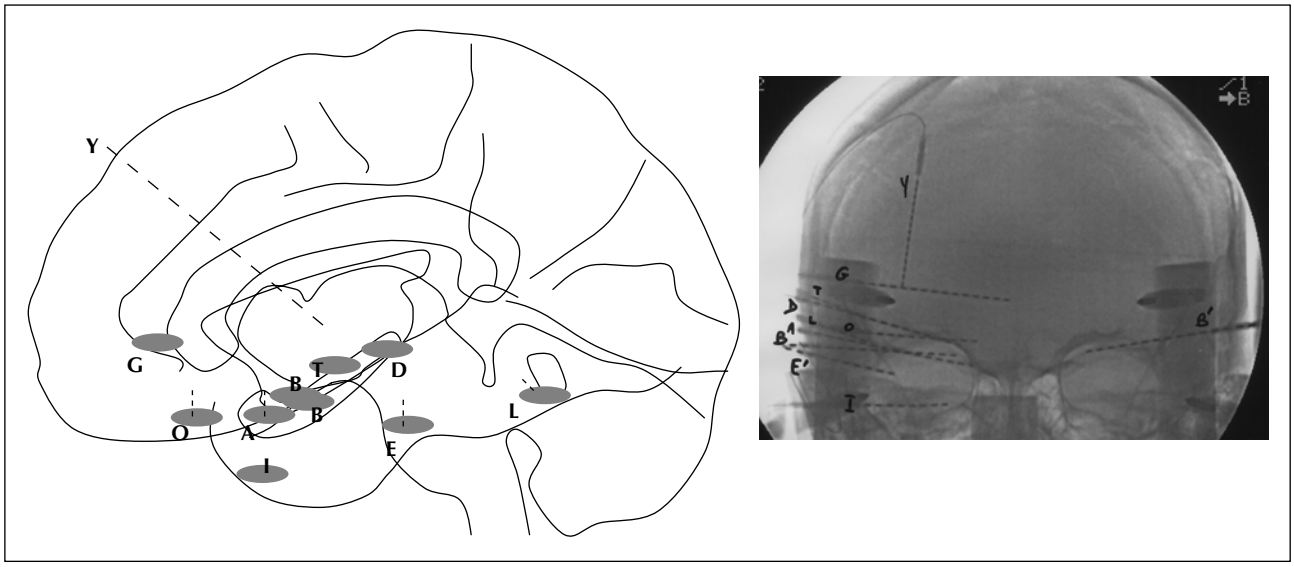


**Figure 8.** Electrodes **Y** investigate the right insula, **O** orbito-frontal region, **L** ¨posterior temporal lesion, **A** right Amygdala, **B, D** right ant. post-hippocampus, **B'** left hippocampus. **I** right temporal pole.

and mesial temporal lobe (pole, hippocampo-amygdalo-parahippocampal cortices), excluding the right temporal posterior scar. Epilepsy surgery of the "actual epileptogenic zone" was performed. Two years after surgery the patient remains seizure-free. □

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